Inflammatory bowel disease, past, present and future: lessons from animal models

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Accumulating data from animal models indicate that inflammatory bowel disease (IBD) is mediated by a much more complicated mechanism than previously predicted. For example, the role of an individual molecule in the pathogenesis of IBD distinctly differs depending on several factors, including the fundamental mechanism of induction of the disease, the target cell type, the phase of disease, and the environment. Therefore, it has been difficult in the past to fully explain the complicated mechanism. Novel concepts have recently been proposed to further explain the complicated mechanism of IBD. In this review, we introduce past, current, and possible future concepts for IBD models regarding T helper (Th) 1, Th2, and Th17, antigen sampling and presentation, regulatory cell networks, NOD2, Toll-like receptors, bacteria/epithelia interaction, stem cells, autophagy, microRNAs, and glycoimmunology, and we also discuss the relevance of these new concepts, developed at the bench (in animal models), to the bedside.

Key words: antigen sampling, autophagy, IBD, Breg, mucin, NOD2, Th17, TLRs

Introduction

Inflammatory bowel disease (IBD), comprising Crohn’s disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disorder caused by multifactorial conditions in a genetically predisposed host. The complicated mechanism underlying IBD is clearly indicated by the presence of many IBD susceptibility genes. Three types of genetically engineered mice, T-cell receptor α (TCRα), interleukin (IL)-2-, and IL-10-knockout (KO) mice were unexpectedly found in 1993, independently by Mombaerts et al., Sadlack et al., and Kuhn et al., to spontaneously develop chronic colitis. Spontaneous development of colitis has since been identified in many kinds of knockout and transgenic mice (Fig. 1). The spontaneous development of colitis in so many different kinds of genetically engineered mice further emphasizes the presence of a more complicated mechanism than previously predicted in the pathogenesis of IBD. Although the animal models of IBD may not fully reflect human IBD, these models have provided us great opportunities to more closely examine the mechanism of this disease. Indeed, animal models not only have contributed significantly during the last decade to our understanding of the complicated mechanism of IBD but also have provided useful interventions for developing novel therapeutic strategies for this disorder. Currently, many animal models of IBD are available, and each model has both merits and disadvantages for studying IBD. For example, acute intestinal injury induced in mice by “continuous” administration of dextran sulfate sodium (DSS) is a useful model for scientifically studying the epithelial barrier and its regeneration and innate immune responses, but it may be an inappropriate IBD model, for example, for evaluating the potency of therapeutic agents in IBD patients.

Th17/IL-23

Accumulating data obtained from experimental IBD models have suggested the involvement of both common and distinct mechanisms in the pathogenesis of UC versus CD. One of the major concepts previously used to explain the different mechanisms is the T helper (Th) 1/Th2 paradigm. Indeed, Th2 cytokines such as IL-4 and IL-13 contribute significantly to chronic UC-like
inflammatory bowel disease; NCAD, nuclear factor of activated T cells; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; TIR8, also known as SIGIRR (single Ig interleukin-1-related receptor); TNP6, transgenic mice lacking TNF AU-rich elements; WASP, Wiskott-Aldrich syndrome protein; XBP1, X-box binding protein

disease. In contrast, the Th1 pathway has been implicated in the pathogenesis of CD. In addition to the Th1/Th2 theory, accumulating recent studies have revealed the critical involvement of the IL-23/IL-17 pathway in the pathogenesis of CD-like experimental diseases. IL-12 (p40/p35) has generally been believed to be a crucial factor involved in the development of Th1-mediated colitis because of the beneficial effect of anti-IL-12p40 treatment in CD patients as well as in Th1-mediated experimental colitis. However, recent studies have demonstrated that IL-23 (a heterodimer of p40 and p19 subunits) rather than IL-12 (a heterodimer of p40 and p35 subunits) contributes to the development of Th1-mediated chronic colitis observed in several murine CD models, including IL-10 KO mice, the CD45RB model, and the cecal bacteria-specific T cell-induced colitis model, and the Helicobacter hepaticus-induced colitis model, and the CD40-dependent innate immune-mediated colitis model. Another very recent study also shows that an IL-23R polymorphism (R381Q) is particularly associated with CD in non-Jewish children. In contrast to Th1-mediated “chronic” colitis, IL-12 rather than IL-23 has been demonstrated to play a pathogenic role in Th1-mediated “acute” colitis, induced by administration of trinitrobenzene sulfonic acid (TNBS).

A current topic in the field of immunology is the discovery of a Th17 T-cell subset characterized by the production of IL-17 (IL-17A) and IL-17F but not interferon (IFN)-γ or IL-4. Differentiation of this Th17 subset is induced through activation of orphan nuclear receptor RORγt signaling, depending on the pleiotropic cytokine transforming growth factor (TGF) β, which is also linked to the development of Foxp3 regulatory T (Treg) cells. Reciprocal Th17 versus Treg cell differentiation is regulated by proinflammatory cytokines such as IL-6 (for differentiation to Th17) and retinoic acid (for differentiation to Treg cells). The expansion and survival of Th17 T cells are subsequently mediated by IL-23 (Fig. 2). IL-17 expression is not detectable in the normal colon of humans, but is readily detectable in

![Fig. 1.](image1)  
**IBD** disease. Inflammation (ellipses) or innate (rectangles) immune pathway. The pathogenesis of colitis in some mouse models has significant contributions from the T helper (Th) 1 or Th2 pathway. IBD, inflammatory bowel disease; IL, interleukin; TGF, transforming growth factor; A20, also known as tumor necrosis factor (TNF)-induced protein 3; CBl-b, E3 ubiquitin ligase; Gα2, G protein α2; GFAP-HA, transgenic mice in which enteric glia are specifically disrupted; GPX, glutathione peroxidase; HLAB27, HLAB27/human β2 microglobulin transgenic rats; LIGHT, a TNF superfamily member; Mdr, multiple drug resistance; Muc2, mucin2; NCAD, transgenic mice that overexpress dominant negative N-cadherin in the intestinal epithelial cells; NEMO, NF-κB essential modulator; NFAT, nuclear factor of activated T cells; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; TIR8, also known as SIGIRR (single Ig interleukin-1-related receptor); TNP6, transgenic mice lacking TNF AU-rich elements; WASP, Wiskott-Aldrich syndrome protein; XBP1, X-box binding protein

![Fig. 2.](image2)  
In the past, the Th1/Th2 paradigm was a major concept in the pathogenesis of acquired immune-mediated colitis. An additional Th17/IL-23 pathway has recently been identified. Interestingly, recent accumulating data have demonstrated the reciprocal developmental pathways for generation of effector Th17 and Foxp3 regulatory T (Treg) cells. Th17 differentiation is induced by TGFβ in the presence of proinflammatory cytokines such as IL-6. In contrast, Treg cell differentiation is induced by TGFβ in the absence of IL-6 and/or presence of retinoic acid (RA). IL-23 is required for the survival and maintenance of Th17. IFN, interferon